REMARKS

Claims 88-116 are currently pending in this application. Claims 91, 93, 94, and 105-116 are withdrawn from examination as allegedly drawn to unelected inventions. Claims 88 and 108 are amended to recite, "wherein the compact particle does not express the detectable entity, and wherein the compact particle is supported by the support medium." Support for those amendments can be found throughout the specification, *e.g.*, at page 27, lines 24-26 and page 44, lines 7-8. Thus, no new matter has been added.

I. REJECTION UNDER 35 U.S.C. § 112, ¶ 2

Claims 88-90, 92, and 95-104 are rejected under 35 U.S.C. § 112, ¶ 2 as allegedly indefinite. (*See* Office Action at p. 4, Items 6-8.) Specifically, the Office contends that "[i]t is unclear due to the grammatical structure of [claim 88] whether 'supported by the medium' is intended to modify 'compact particle' or 'detectable entity'. As such, it is unclear whether Applicant intends that the compact particle, or only the detectable entity is supported by the medium." (*Id.* at Item 8.)

Without acquiescing to the rejection, and solely to facilitate prosecution, claim 88 is amended herein to recite the phrase "wherein the compact particle is supported by the support medium." Applicant submits that the currently amended claims are definite and respectfully requests that the Office withdraw the rejection of claims 88-90, 92, and 95-114 under 35 U.S.C. § 112.

II. REJECTION UNDER 35 U.S.C. § 102

Claims 88-90, 92, 95, 96, and 98-103 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,610,022 to Battifora ("*Battifora*"). (*See* Office Action at pp. 4-5, Items 9 and 10.) Specifically, the Office contends that "[t]he instant

specification defines the term 'attached' so as to encompass any association between the detectable entity and the compact particle, e.g. intracellular detectable entities (see page 64, lines 1-14 and page 52), such that the target molecules expressed by cells as in Battifora et al. would be considered to be 'attached' to the cells." (*Id.* at p. 5.)

Without acquiescing to the rejection, and solely to facilitate prosecution, claim 88 is amended herein to recite the phrase "wherein the compact particle does not express the detectable entity." In contrast, *Battifora* discloses an internal control for immunocytochemistry assays "comprising cells ... that express a known amount of a target molecule such as estrogen or progesterone receptor...." (Office Action at pp. 4-5.) Accordingly, *Brattifora* cannot anticipate the instantly claimed invention because it fails to expressly or inherently teach each and every limitation set forth in the currently amended claims. (*See* M.P.E.P. § 2131, 8th Ed., July 2008 Rev.)

For at least these reasons, Applicant respectfully requests that the Office withdraw the rejection of claims 88-90, 92, 95, 96, and 98-103 under 35 U.S.C. § 102(b).

III. REJECTIONS UNDER 35 U.S.C. § 103

A. Claim 97

Claim 97 is rejected under 35 U.S.C. § 103 as allegedly obvious over *Battifora* in view of Harvey Lodish, Molecular Cell Biology 4th Ed. §§ 17.5, 23.4, and 23.7 (W. H. Freeman and Company 1986) (2000) ("*Lodish*"). (*See* Office Action at pp. 6-8, Item 13.) Specifically, the Office acknowledges that *Battifora* "fails to specifically teach that the detectable entitites (target molecules/antigens) include those that are covalently attached to the compact particle (cell)" but contends that *Lodish* cures these deficiencies in *Battifora* because "Lodish et al. teach that there are a vast array of integral membrane proteins, and

that some of these proteins are covalently attached to the membrane via a GPI anchor ...." (*Id.* at pp. 6 and 7.)

Although Applicant disagrees with the Office's characterization of GPI-modified proteins[1], as discussed above, *Battifora* does not expressly or inherently teach "[a] reference standard for a detectable entity ... comprising a compact particle ... wherein the compact particle does not express the detectable entity," as required by claim 88, from which claim 97 depends. *Lodish* fails to cure these deficiencies in *Battifora* because *Lodish* does not teach or suggest reference standards at all, let alone "[a] reference standard ... comprising ... a quantity of detectable entity attached to [a] compact particle, wherein the compact particle does not express the detectable entity," as recited in the currently pending claims. Thus, the Office has failed to establish a *prima facie* case of obviousness because one of skill in the art cannot arrive at the instantly claimed invention merely by combining the GPI anchors disclosed in *Lodish* with the internal controls disclosed in *Battifora*.

For at least these reasons, Applicant respectfully requests that the Office withdraw the rejection of claim 97 under 35 U.S.C. § 103.

B. Claim 104

Claim 104 is rejected under 35 U.S.C. § 103 as allegedly obvious over *Battifora* in view of O'Leary T.J., "Standardization in Immunohistochemistry," Applied Immunohistochemistry & Molecular Morphology, 9:3-8 (2001) ("*O'Leary*"). (*See* Office Action at pp. 8-9, Item 14.) Specifically, the Office acknowledges that *Battifora* "fails to specifically teach the inclusion of a positive control that comprises a compact particle with substantially no detectable entity" but contends that *O'Leary* cures these deficiencies in

[1] Although GPI moieties are attached to proteins through covalent bonds (*see Lodish* at section 17.5 and *Stryer*),GPI-modified proteins attach to cell membranes through hydrophobic (not covalent) interactions between the GPI moiety and plasma membrane lipids. *See Stryer* at Figure 35-32 ("The two fatty acyl chains linked to the glycerolphosphate unit serve as membrane anchors.").

Battifora because "O'Leary et al. relates to standardization of immunohistochemical analysis, and teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible ...." (*Id.* at p. 8.)

As discussed above, *Battifora* fails to expressly or inherently teach "[a] reference standard for a detectable entity ... comprising a compact particle ... wherein the compact particle does not express the detectable entity," as required by claim 88, from which claim 104 depends. *O'Leary* fails to cure these deficiencies in *Battifora* because although *O'Leary* discusses a need for reference standards in immunohistochemistry assays (*see* section titled "Conclusions and Recommendations"), *O'Leary* does not teach or suggest that such reference standards should comprise "a quantity of detectable entity attached to [a] compact particle, wherein the compact particle does not express the detectable entity," as recited in the currently pending claims. Thus, the Office has failed to establish a *prima facie* case of obviousness because one of skill in the art cannot arrive at the instantly claimed invention merely by combining the internal controls disclosed in *O'Leary* with the internal controls disclosed in *Battifora.*

For at least these reasons, Applicant respectfully requests that the Office withdraw the rejection of claim 104 under 35 U.S.C. § 103.

IV. DOUBLE PATENTING REJECTIONS

A. U.S. Patent Application No. 10/547,033

Claims 88-90, 92, 95-97, and 98-104 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-32 and 35-41 of copending U.S. Patent Application No. 10/547,033 ("the '003 application") in view of *Battifora* alone, or in combination with *Lodish* or *O'Leary*. (*See* Office Action at pp.

10-12, Items 16-18.) Specifically, the Office acknowledges that the '033 application does not currently claim "that the detectable entity is attached [covalently or otherwise] to a compact particle such as a cell," or "the inclusion of a positive control that comprises a compact particle with substantially no detectable entity,"[2] but contends that *Battifora*, *Lodish*, and *O'Leary* cure these deficiencies in the '033 application because *Battifora* allegedly "teaches reference standards that include detectable entity provided in the context of cells (i.e., compact particles)," *Lodish* allegedly teaches "GPI-anchored proteins (which are covalently attached to cells)," and *O'Leary* allegedly "teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible." (*Id.*)

As the Office acknowledges, claims 1-32 and 35-41 of the '033 application do not disclose "[a] reference standard ... comprising ... a quantity of detectable entity attached to [a] compact particle, wherein the compact particle does not express the detectable entity," as recited in the currently amended claims. For the reasons discussed above, *Battifora*, *Lodish*, and *O'Leary* also do not teach or suggest these elements of the instant invention and, therefore, fail to cure the deficiencies in the '033 application. Thus, the Office has not established a *prima facie* case of provisional obviousness-type double patenting because one of skill in the art cannot arrive at the instantly claimed invention merely by combining claims 1-32 and 35-41 of the '033 application with the teachings of *Battifora*, *Lodish*, and *O'Leary*.

For at least these reasons, Applicant respectfully requests that the Office withdraw the provisional double patenting rejection of claims 88-90, 92, 95-97, and 98-104.

[2] However, Applicant notes that the specification of the '033 application does disclose such controls, for example, in paragraph [0220] of the published application.

B. U.S. Patent Application No. 11/884,247

Claims 88-90, 92, 95, 96, and 98-104 are rejected on the ground of provisional nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-26, 31, 33-40, 44, 45, and 48-52[3] of copending U.S. Patent Application No. 11/884,247 ("the '247 application") alone, or in view of *O'Leary*. (*See* Office Action at pp. 12-14, Items 19-20.) With respect to claims 88-90, 92, 95, 96, and 98-103, the Office contends that "Application No. 11/884,247 also claims a matrix (i.e., support medium) in which microparticles or cells may be embedded (see, e.g., claims 1 and 34-36). The microparticles or cells are associated with (i.e., attached to) detectable entities ("antigens") such as CD3 or CD4 (see claims 15 and 34-36)." (*Id.* at pp. 12-13.) With respect to claim 104, the Office acknowledges that "[t]he claims of the copending application ... do not recite a positive control that comprises a compact particle with substantially no detectable entity," but contends that *O'Leary* cures these deficiencies in the '247 application because *O'Leary* allegedly "teaches that the interpretation of immunohistochemical stains should be guided by the staining of appropriate positive, negative, and internal controls whenever possible." (*Id.* at p. 13.)

Even assuming, *arguendo*, that the Office has properly interpreted the terms "microparticles" and "cell binding agent" in claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application to read on the terms "compact particle" and "detectable entity," respectively, in the currently pending claims, Applicant notes that claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application do not recite that the "cell binding agent" (*i.e.*, "detectable entity")

[3] Item 19 on page 12 of the Office Action recites that claims 88-90, 92, 95, 96, and 98-103 are rejected over "claims 1-26, 31, 33-40, 44-45, and 48-52 of copending Application No. 11/884,247," while Item 20 on page 13 of the Office Action recites that claim 104 is rejected over "claims 1-32 and 35-41 of copending Application No. 11/884,247 in view of O'Leary et al." Since claims 27-30, 32, 38, 41-43, 46, and 47 have been canceled from the '247 application, Applicant assumes the Office intended to refer to the same set of claims from the '247 application in both rejections.

is attached to the "microparticles" (*i.e.*, "compact particle"), as required by the currently pending claims. Instead, the "cell binding agent" of claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application is attached to "a container" or "an apparatus," which are not equivalent to the compact particles of the instant invention. (*See, e.g.*, claims 1 and 34 of the '247 application.) Thus, the Office has failed to establish a *prima facie* case of obviousness because claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application do not teach or suggest "a compact particle comprising a quantity of detectable entity attached to the compact particle," as recited in the currently pending claims.

O'Leary fails to cure these deficiencies in claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application because although *O'Leary* discusses a need for reference standards in immunohistochemistry assays (*see* section titled "Conclusions and Recommendations"), *O'Leary* does not teach or suggest that such reference standards should comprise "a quantity of detectable entity attached to [a] compact particle, wherein the compact particle does not express the detectable entity." Thus, the Office has failed to establish a *prima facie* case of provisional obviousness-type double patenting because one of skill in the art cannot arrive at the instantly claimed invention merely by combining claims 1-26, 31, 33-40, 44, 45, and 48-52 of the '247 application with the teachings of *O'Leary*.

For at least these reasons, Applicant respectfully requests that the Office withdraw the provisional double patenting rejection of claims 88-90, 92, 95, 96, and 98-104.

V. REJOINDER

In view of the amendments and arguments presented herein, Applicant respectfully submits that the elected invention of reference standards and the elected species of cells are allowable over the prior art. Thus, in accordance with 37 C.F.R. §§ 1.104 and 1.141, Applicant respectfully requests that the Office rejoin the withdrawn process claims and

extend examination to the unelected species of compact particles to the extent necessary to find the generic claims allowable.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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Attachments: Lubert Stryer, Biochemistry 4th Ed. 935 (W. H. Freedman and Company 1975) (1995) ("*Stryer*")

Biochemistry

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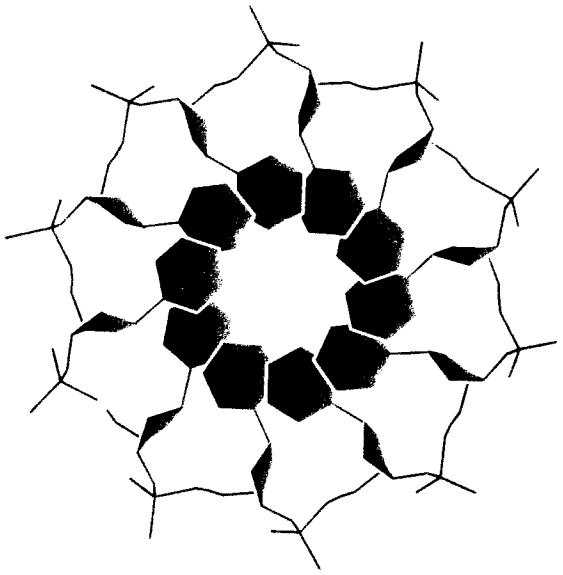

Lubert Stryer

STANFORD UNIVERSITY

W. H. Freeman and Company

New York

Library of Congress Cataloging-in-Publication Data

Stryer, Lubert.
Biochemistry/Lubert Stryer.—4th ed.

Includes index.
ISBN 0-7167-2009-4
1. Biochemistry. I. Title.
QP514.2.S66 1995
574.19'2—dc20 94-22832

Printed in the United States of America

Seventh printing, 1999

GLYCOSYL PHOSPHATIDYL INOSITOL UNITS SERVE AS MEMBRANE ANCHORS FOR MANY CELL-SURFACE PROTEINS

A different molecular device is used to anchor a protein in the *outer* leaflet of the plasma membrane. *Glycosyl phosphatidyl inositol (GPI)* (Figure 35-32) attached to the carboxy terminus of a protein serves as a *flexible leash* that gives it freedom to act on molecules outside the cell. The entire protein except for this glycolipid anchor is located in the extracellular space. Many cell-surface hydrolytic enzymes and adhesins are tethered to the cell by a GPI unit.

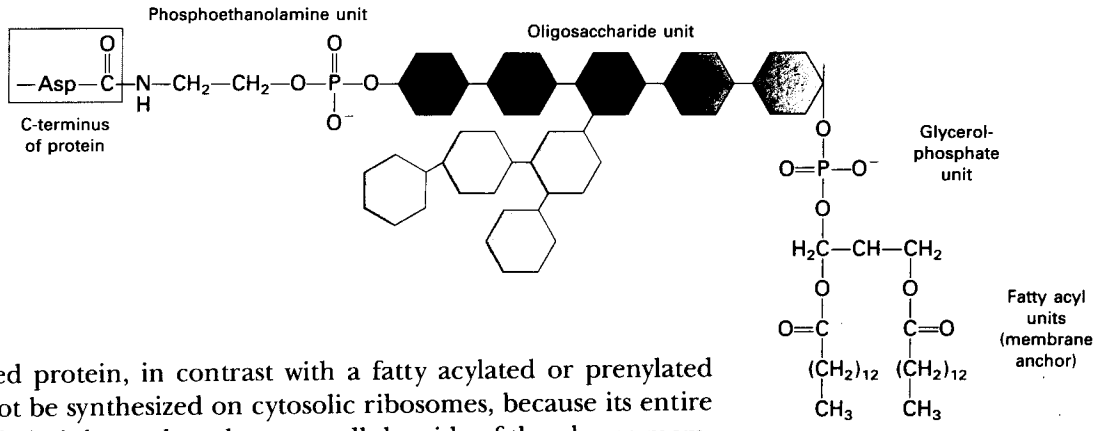

Figure 35-32
Glycosyl phosphatidyl inositol (GPI) units anchor many cell-surface proteins to the outer leaflet of the plasma membrane. The carboxy terminus of the protein is attached to the phosphoethanolamine unit of GPI. The oligosaccharide unit is schematically represented by a series of hexagons (mannose in green, galactose in yellow, *N*-acetylglucosamine in blue, and inositol in red). The two fatty acyl chains linked to the glycerolphosphate unit serve as membrane anchors. [After T.L. Doering, W.J. Masterson, G.W. Hart, and P.T. Englund. *J. Biol. Chem.* 265(1990):611.]

A GPI-linked protein, in contrast with a fatty acylated or prenylated protein, cannot be synthesized on cytosolic ribosomes, because its entire polypeptide chain is located on the extracellular side of the plasma membrane. Rather, GPI-anchored proteins initially contain an N-terminal signal sequence that directs the nascent chain to the ER, and a C-terminal hydrophobic sequence 20 to 30 residues long. This hydrophobic C-terminal region transiently ties the protein to the ER membrane. The ethanolamine end of a preformed GPI unit then attacks a peptide bond at the lumenal end of this C-terminal tether. The C-terminal peptide is released, and a GPI-anchored protein is generated. This protein then goes from the ER to the Golgi and then to the plasma membrane, the default destination.

SPECIFIC PROTEINS ARE IMPORTED INTO CELLS BY RECEPTOR-MEDIATED ENDOCYTOSIS

We turn now to a different facet of protein targeting—the import of specific proteins into a cell by their binding to receptors in the plasma membrane and their inclusion into vesicles. This process of *receptor-mediated endocytosis* (Figure 35-33) has broad biological significance. First, it is

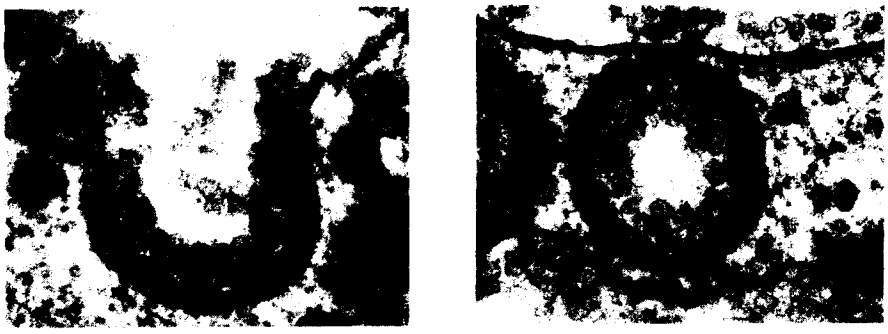

Figure 35-33
Receptor-mediated endocytosis takes place at coated pits in the plasma membrane. These electron micrographs show the uptake of vitellogenin, a lipoprotein, by hen oocytes [Courtesy of Dr. M.M. Perry and Dr. A.A. Gilbert.]